Physiologically Based Pharmacokinetic Models And Biologically Based Pharmacodynamic Models

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Go here to learn more about ACSL (simulation language)

MODEL 1: LACTATIONAL TRANSFER OF TETRACHLOROETHYLENE AND CANCER RISK ASSESSMENT FOR INFANT

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For LACTMAN.CSL file click here

For LACTMAN.CMD file click here
'Key words: Physiologically based pharmacokinetic model, PBPK, '
' Tetrachloroethylene, PERC, PCE, Cancer risk assessment, '
' Breast-fed infant, Toxicology, ACSL. '

' Description of this program has been published: Byczkowski,J.Z., '
' and Fisher,J.W. (1995) A computer program linking physiologically '
' based pharmacokinetic model with cancer risk assessment for '
' breast-fed infants. Computer Methods Progr. Biomed. 46, 155-163. '
' Reprints of this article are indicated as AL/OE-TR-1995-0014 by '
' Armstrong Aerospace Medical Research Laboratory, Wright Patterson '
' Air Force Base, OH. '
' Results of simulation have been published: Byczkowski,J.Z. (1996) '
' A linked pharmacokinetic model and cancer risk assessment for '
' breast-fed infants. Drug Information J. 30, 401-412. '
' Reprints of this article are indicated as AL/OE-TR-1996-0007 by '
' Armstrong Aerospace Medical Research Laboratory, Wright Patterson '
' Air Force Base, OH. '

MODEL 2: LINEAR MODEL FOR CADMIUM INHALATION

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For KNOB.CSL file click here
'Key words: Linear pharmacokinetic model, PK, '
' Cadmium, Cd, Inhalation, Risk assessment, '
' Toxicology, ACSL. '

'An ACSL version of the Kjellström and Nordberg's PK linear model for'
'inhalation exposure to cadmium. '
'Description of this program has been published: Byczkowski,J.Z.: '
'Pharmacokinetic/Dynamic Modeling. In: Standard Handbook of '
'Environmental Science, Health and Technology, Chapter 8.6 '
'(Lehr, J. Ed), McGraw-Hill, New York, 2000. '

MODEL 3: LIPID PEROXIDATION IN LIVER SLICES

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For LPOXLIV.CSL file click here

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Source: https://www.industrydocuments.ucsf.edu/docs/fsdj0001

For LPOXLIV.CMD file click here
'Key words: Biologically based pharmacodynamic model, BBPD, Liver '
' in vitro, Lipid peroxidation, Toxicology, tert-Butyl hydroperoxide,'
' Bromotrichloromethane, Mouse, Rat, ACSL. '

' Description of this program has been published: Byczkowski,J.Z., '
' Channel,S.R., Pravecek,T.L., and Miller,C.R. (1996) '
' Mathematical model for chemically induced lipid peroxidation in '
' precision-cut liver slices: Computer simulation and experimental '
' calibration. Computer Methods Progr. Biomed. 50, 73-84. '
' Reprints of his article are indicated as AL/OE-TR-1996-0081 by '
' Armstrong Aerospace Medical Research Laboratory, Wright Patterson '
' Air Force Base, OH. '
' Results of simulation and experimental details have been '
' published: Byczkowski,J.Z., Channel,S.R., and Pravecek.L. (1995). '
' Development and experimental calibration of the mathematical '
' model for lipid peroxidation in mouse liver slices. Reprints of '
' this article are indicated as Technical Report, AL/OE-TR-1995-0179'
' by Armstrong Aerospace Medical Research Laboratory, Wright '
' Patterson Air Force Base, OH. '

MODEL 4: TCE - INITIATED LIPID PEROXIDATION IN LIVER SLICES

DOWNLOAD MODEL FILE WRITTEN IN ACSL

For LPOTCE.CSL file click here
'Key words: Biologically based pharmacodynamic model, BBPD, Liver, '
' in vitro, Lipid peroxidation, Toxicology, Trichloroethylene,'
' TCE, Mouse, TBARS, Thiobarbituric acid reactive substances, ACSL'

' Description of this program has been published: Byczkowski,J.Z., '
' Channel,S.R., and Miller,C.R. (1999) '
' A Biologically Based Pharmacodynamic Model for Lipid Peroxidation '
' Stimulated by Trichloroethylene In Vitro. '
' Journal of Biochemical and Molecular Toxicology. 13, 205-214. '

EXAMPLE *.CSL FILE OF BBPD MODEL 3 WRITTEN IN ACSL

PROGRAM: LIPID PEROXIDATION
'Version 2 *SQRT* (original model: Byczkowski et al. Comp. Meth'
'Progr. Biomed. 50, 73, 1996), based on mathematical description'
'by Tappel et al. Free. Rad. Biol. Med. 7, 361, 1989. '
'THE PURPOSE OF THIS PROGRAM IS TO SIMULATE PRODUCTION OF TBARS'
'FROM PUFA IN MOUSE LIVER SLICES in vitro. **DEFAULT FOR TCE***'
'DESCRIPTION: Byczkowski et al. J. Biochem. Mol. Toxicol. 13, 205, 1999.'

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Source: https://www.industrydocuments.ucsf.edu/docs/fsdj0001

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INITIAL

'PEROXIDATION PARAMETERS FOR TCE IN LIVER [0.1 g of liver] '
CONSTANT IND1 = 1.0 $'inducer 1 [mcM TCE/0.1g liv] '
CONSTANT PUF = 7.0 $'Conc.PUFA[microMol/0.1 g liver]'
CONSTANT PXZLUF= 12.0 $'peroxidizability of PUFA-L[1/h]'
CONSTANT PXZHUF= 24.0 $'peroxidizability of PUFA-H[1/h]'
CONSTANT ANOX1 = 0.0037 $'Vit.E antiox[microMol/0.1g liv]'
CONSTANT ACT1 = 0.0003 $'activator1[mcM cytP450/0.1gliv]'
CONSTANT GSH = 0.6 $'glutathione [mcroM/0.1 g liver]'
CONSTANT PXTTBA= 0.1 $'yield ofTBARS/Mol hydroperoxide'
CONSTANT LPUF = 3. $'LA-derivative PUFA[mcMol/0.1 g]'
CONSTANT HPUF = 4. $'HA-derivative PUFA[mcMol/0.1 g]'
CONSTANT EFANO1 = 1. $'effectiveness of Vit.E '
CONSTANT ANOXUF = 2. $'antioxidant use factor [/mcmol]'
CONSTANT ANOX2 = 0. $'non-Vit.E antiox[mcM/0.1 g liv]'
CONSTANT ANOX3 = 0. $'added antioxidant[mcM/0.1g liv]'
CONSTANT ACACT1 = 1. $'activity of activator 1 '
CONSTANT ACTDGF = 0.0014 $'activator degradation fctr /mcm'
CONSTANT PTIND1 = 250. $'potency of inducer 1 [1/mcmol] '
CONSTANT INDLF = 0.0001 $'inducer loss factor [1/h] '
CONSTANT PXRATE = 0.00029 $'peroxidation rate [mcm/mcm] '
CONSTANT AUTOXF = 0.00013 $'autooxidation factor [1/h] '
CONSTANT GPENZA = 1. $'glutathione peroxidase[/mcM] '
CONSTANT PXREDF = 0.17 $'hydroperoxide reduction fctr /h'
CONSTANT TSTOP = 2. $'end of simulation [h] '
CONSTANT ACR = 0.025 $'Activator degradation rate[1/h]'
CONSTANT PHYSPX = 0. $'physiological levels of Hperox '
CONSTANT ANREG = 0. $'antioxidant regenerated in situ'
CONSTANT BCKGD = 0.0 $'TBARS in control [mcm/0.1 g] '

!PARAMETERS FOR EXPOSURE TO SECOND CHEMICAL PROOXIDANT
CONSTANT EFANO2 = 0. $'effectiveness of non-Vit.E a-o '
CONSTANT EFANO3 = 0. $'effectiveness of added a-o '
CONSTANT ACT2 = 0. $'activator 2 [mcM/0.1 g liver] '
CONSTANT ACACT2 = 0. $'activity of activator 2 '
CONSTANT IND2 = 0. $'inducer2[mcM chemical/0.1g liv]'
CONSTANT PTIND2 = 0. $'potency of inducer 2 [1/mcmol] '

'TIMING COMMANDS '
CONSTANT POINTS = 500.
CINT=TSTOP/POINTS

' INITIALIZATION '
'RESETS INITIAL CONDITIONS BEFORE PEROXIDATION '
CONSTANT ACTLOS=0. $'activator loss '
CONSTANT AUTOX =0. $'autooxidation '
CONSTANT PXREDG=0. $'Hperoxides red. by GSH peroxidase'
CONSTANT PXLUF =0.00199 $'L-Hydroperoxides formed '
CONSTANT PXHUF =0.0053 $'H-Hydroperoxides formed '
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CONSTANT PXREM =0. $'accumulated remaining Hperoxides '
CONSTANT TPX =0. $'accumlted total Hperoxides formed'
CONSTANT ILR =0. $'rate of inducer loss = 0. '

END $'End of Initial '

DYNAMIC
ALGORITHM IALG = 2 $'Gear stiff method '

DERIVATIVE

PROCEDURAL

IF (LPUFRE.LE.0) LPUFRE = 0.
IF (HPUFRE.LE.0) HPUFRE = 0.
IF (ACTLOS.GE.ACTEF) ACTLOS = ACTEF
IF (ANOXRE.LE.1.e-10) ANOXRE = 1.e-10
IF (GSHREM.LE.0) GSHREM = 0.
IF (INDLOS.GE.INDEF) INDLOS = INDEF
IF (PXREDA.GE.TPX) PXREDA = TPX

END $'End of procedural '

'-----------------------------------------------------------------'
'#s Correspond to equations in Tappel et al. (1989) and '
' Byczkowski et al. (1996) '
!VARIABLES ARE CONVERTED TO CONCENTRATIONS [micromole/0.1 g liver]
'-----------------------------------------------------------------'

'1. Remaining polyunsaturated fatty acids '

LPUFRE = LPUF - PXLUFA - AUTOXA/2
HPUFRE = HPUF - PXHUFA - AUTOXA/2

'2. Effective activator '

ACTEF = ACT1*ACACT1 + ACT2*ACACT2

'3. Activator loss '

ACTLOS = ACTEF*ACTDGF*TPX

'4. Remaining activator '

ACTREM = (ACTEF - ACTLOS)*exp(-ACR*INDREM*t)

'5. Effective inducer '

INDEF = SQRT(IND1*PTIND1) + IND2*PTIND2
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'6. Remaining inducer '

INDREM = INDEF - INDLOS

'6.a. Inducer loss rate '

ILR = INDEF*INDLF

'7. Activated inducer '

ACTIND = INDREM*ACTREM

'8. Effective antioxidant '

ANOXEF = ANOX1*EFANO1 + ANOX2*EFANO2 + ANOX3*EFANO3

'9. Remaining antioxidant '

ANOXRE = ANOXEF - ANOXEF*TPX*ANOXUF + ANREG*exp(-ANOXR*t)

'10.Hydroperoxides formed by action of activated inducer on '
' PUFA'

PXLUF = LPUFRE*PXZLUF*ACTIND*PXRATE/ANOXRE
PXHUF = HPUFRE*PXZHUF*ACTIND*PXRATE/ANOXRE

'12.Autooxidation '

AUTOX = (LPUFRE + HPUFRE)*AUTOXF*TPX/ANOXRE

'14.Accumulated total hydroperoxides formed '

TPX = AUTOXA + PXLUFA + PXHUFA + PHYSPX

'15.Remaining glutathione '

GSHREM = GSH - PXREDA

'16.Hydroperoxides reduced by glutathione peroxidase '

PXREDG = PXREM*GPENZA*GSHREM*PXREDF

'18.Accumulated remaining hydroperoxides '

PXREM = TPX - PXREDA

'19.Amount of TBARS from accumulated remaining hydroperoxides '

TBARS = PXREM*PXTTBA + BCKGD

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'6b. Inducer lost over time '

INDLOS = INTEG(ILR,0.)

'11.Accumulated hydroperoxides formed by action of activated '
' inducer on PUFA '

PXLUFA = INTEG(PXLUF, 0.)

PXHUFA = INTEG(PXHUF, 0.)

'13.Accumulated autooxidation '

AUTOXA = INTEG(AUTOX, 0.)

'17.Accumulated hydroperoxides reduced by glutathione '
' peroxidase'

PXREDA = INTEG(PXREDG, 0.)
'--------------------------------'
TERMT(T.GE.TSTOP) $'Termination at TSTOP '
END $'End of derivative '
END $'End of dynamic '
'^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^'
TERMINAL $'Resets parameters to initial values'
ACTREM = ACTEF
INDREM = INDEF
ANOXRE = ANOXEF
END $'End of terminal '
'^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^^'
END $'End of program '
```

Please send comments to the author E-mail address:
JANUSZ.BYCZKOWSKI@USA.NET

'--'

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